Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

Upon entry of the foregoing amendment, claims 35-37 and 39-45 are pending in the application, with 35 and 40 being the independent claims. Claims 35 and 40 are sought to be amended to more clearly describe the Applicant's invention. Claim 38 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. The foregoing amendments are made to place the application in a better condition for allowance or appeal and will not require any additional consideration or search. These changes are believed to introduce no new matter and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Information Disclosure Statements

In the Amendment and Reply filed May 14, 2007, Applicants noted that the Examiner returned an initialed copy of the PTO-1449 form submitted with the First Supplemental Information Disclosure Statement filed May 9, 2005, but did not initial next to document AK1 (U.S. Patent No. 5,236,904). Applicants respectfully request that the Examiner return another copy of the PTO-1449 form indicating that this document has been considered.

Applicants also noted in the Amendment and Reply filed May 14, 2007, that an initialed copy of the PTO-1449 form submitted with the Fourth Supplemental Information Disclosure Statement filed December 19, 2006 had not been returned. Applicants respectfully request that the Examiner return a copy of the PTO-1449 form indicating that the cited documents have been considered.

III. Rejection of Claims 35-45 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 35-45 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,416,323 to Grenfell, W.W., *et al.* (hereinafter "Grenfell") in view of U.S. Patent No. 4,659,714 to Watt-Smith, S.R. (hereinafter "Watt-Smith"). (Office Action, page 2, lines 16-17). Applicants respectfully traverse the rejection.

The Examiner is of the opinion that Grenfell teaches a dental cartridge that fits into a standard dental local anesthetic syringe, that Watt-Smith teaches the use of phentolamine or its salts to improve local anesthesia for dentistry or oral surgery, and that it would have been obvious to put phentolamine mesylate into the syringe of Grenfell. (Office Action, pages 2-3). Applicants respectfully disagree.

The present application is directed to a dental cartridge containing a composition consisting essentially of about 0.0018 mg to about 0.45 mg phentolamine mesylate or a molar equivalent of another alpha adrenergic receptor antagonist and a pharmaceutically acceptable carrier (claim 35) or containing a composition consisting essentially of an alpha adrenergic receptor antagonist at a concentration of from about 0.001 mg/mL to

about 0.25 mg/mL (claim 40). Additionally, the dental cartridge has a volume of between 1.6 mL to 1.8 mL.

Grenfell teaches a self-shielding dental syringe and methods for using the syringe (see Abstract). The syringe disclosed has a body for receiving a dental cartridge which is "generally pre-filled with medicine, such as an anaesthetic, vaccine or other therapeutic or diagnostic agent." (Grenfell, column 7, lines 50-52). The Examiner asserts that the "cartridge contains a composition comprising substances to improve local anesthesia for dentistry or oral surgery." (Office Action, page 2, lines 22-23). However, the improvement is the addition of a shield for selectively covering the needle of the syringe after medication is dispensed from it. Grenfell neither discloses any specific compositions nor are any formulations or concentrations provided. Therefore, the dental cartridge of Grenfell may contain an anesthetic but there is no teaching that an alpha adrenergic receptor antagonist may be present, much less in an amount of about 0.0018 mg to about 0.45 mg in a volume between 1.6 mL and 1.8 mL.

Watt-Smith discloses the application of an alpha adrenoreceptor blocking agent in an amount sufficient to reduce the prolongation from the co-application of a anesthetic agent and a vasoconstrictor (see Abstract). Watt-Smith discloses a dose response experiment where doses at concentrations of 1 to 3 mg/mL were tested; the higher doses and concentrations were found to be more effective in reducing the duration of anesthesia. (Column 6, lines 5-28, Example 1 and Table I). The additional examples disclosed in Watt-Smith utilize phentolamine doses at a concentration of 2 mg/mL. The disclosure strongly indicates that higher doses and concentrations of phentolamine are preferred. For example, Watt-Smith discloses that the alpha adrenoreceptor blocking

agent is administered to the body in "an amount sufficient *substantially* to reduce or reverse the prolongation" (Column 2, lines 11-13, emphasis added) and "to cause *substantial* reduction or reversal of the prolongation of anesthetic effect." (Column 5, lines 1-3, emphasis added). Therefore, as Table I indicates that higher concentrations of phentolamine cause a more *substantial* reduction in the reversal of prolongation, Watt-Smith teaches away from the use of lower doses and concentrations.

The Examiner alleges that one would have been motivated to "substitute Grenfell's claimed active ingredient substance" with the phentolamine taught by Watt-Smith. (Office Action, page 3, lines 8-10). Additionally, the Examiner cites to M.P.E.P. Section 2114.06 that "it is *prima facie* obvious to combine two or more compositions each of which is taught by the prior art to be useful for the same purpose (e.g. to improve local anesthesia for dentistry or surgery) in order to form a third composition to [be] used for the same purpose." (Office Action, page 3, lines 15-18). Applicants respectfully disagree.

Grenfell does not disclose a *composition* that is useful for the purpose of improving local anesthesia for dentistry or surgery. Grenfell discloses a self-shielding dental syringe, however, the only mention of a composition is that the dental cartridge "is generally pre-filled with medicine, such as an anaesthetic, vaccine or other therapeutic or diagnostic agent." (Column 7, lines 50-52). Therefore, as Grenfell does not teach an alpha adrenergic receptor antagonist that is useful for improving local anesthesia for dentistry or surgery, M.P.E.P. Section 2114.06 does not apply.

The Examiner also alleges that according to Table I in Watt-Smith (column 6, lines 14-22) most of the reduction of the prolonged anesthetic effect takes place between

0 mg/mL to 1 mg/mL and that between 1 mg/mL and 3 mg/mL "the reduction of the prolonged anesthetic appears to be approximately linear and only slightly changing." (Office Action, page 3, lines 20-22). Applicants respectfully disagree.

Firstly, Watt-Smith discloses concentrations of phentolamine in Table I not unit doses (column 6, lines 14-22). Therefore, the 1, 1.4, 2.0 and 3.0 mg/mL concentrations tested in Watt-Smith should be compared to the concentrations, rather than the unit doses, that can be calculated as 0.001 mg/mL (0.0018 mg/1.8 mL) to about 0.25 mg/mL (0.45 mg/1.6 mL) from claim 35 and which are set forth in claim 40.

Secondly, dose-response curves can have almost any shape, however, most dose-response curves will have a hyperbolic/sigmoid shape. (see GraphPad Software, "Introducing dose-response curves," http://www.curvefit.com/introduction89.com (1999)(page 1, line 29, through page 2, line 1)(Exhibit A, attached hereto). Therefore, the curve is expected generally not to be linear and experimentation is necessary to determine the dose-response curve. Thus, one cannot predict the duration of anesthesia by using less than the 1 mg/mL of phentolamine disclosed by Watt-Smith.

Thirdly, determination of the optimal dosage for phentolamine based on the disclosure of Watt-Smith is exacerbated by the prior co-administration of an anesthetic agent and a vasoconstrictor. One cannot merely determine the dose-response curve for phentolamine but must also consider the dose-response curves for the anesthetic agent and the vasoconstrictor and how these three drugs effect each other.

Fourthly, there is no reason for using a concentration that is four-fold less than the lowest amount disclosed in Watt-Smith of 1 mg/mL. Similarly, in *In re Wiggens*, 397 F.2d 356 (CCPA 1968), the court held that claims to a pharmaceutical preparation

comprising an old compound at a specified amount were not obvious over a prior art reference teaching the same compound in an amount that was four-fold less than the claimed amount. *Id.* at 359. Furthermore, by disclosing that a substantial reduction in the reversal of prolongation is desired, Watt-Smith teaches away from using a lower dosage than what is disclosed in Table I.

Therefore, based on the amendments to the claims and the reasons provided, Applicants respectfully request that the rejection of claims 35-45 under 35 U.S.C. § 103(a) be withdrawn.

IV. Examiner's Response to Arguments

In response to the Applicant's previous arguments, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify Watt-Smith's phentolamine amount "because according to Watt-Smith Table 1, a claimed amount under 1 mg has nearly the same beneficial effect of the reduction of the prolonged anesthetic effect as an amount over 1 mg which has a nearly linear response to the amount of phentolamine between 1 and 3 mg." (Office Action, page 5, lines 3-8). Applicants respectfully disagree.

As stated in Section III, a determination of the desired dose of phentolamine is not obvious. Not only are most dose-response curves not linear but in Watt-Smith, the effects of the anesthetic agent and vasoconstrictor also must be considered. Furthermore, Watt-Smith teaches away from the use of lower doses and concentrations by disclosing that a substantial reduction or reversal of the prolongation is desired.

Additionally, the Examiner alleges that one of ordinary skill in the art would have been motivated to "substitute Grenfell's claimed active ingredient substance within its claimed dental cartridge with the active ingredient of a phentolamine or its salts as taught by Watt-Smith because the above combined two references as a whole would create the claimed invention's dental cartridge." (Office Action, page 5, line 21, through page 6, line 2). Applicants respectfully disagree.

As stated in Section III, Grenfell discloses that the dental cartridge may contain an anesthetic but there is no teaching that an alpha adrenergic receptor antagonist may be present. Here, the Examiner has not pointed to any particular reason why one of ordinary skill in the art would replace the anesthetic, vaccine or other therapeutic or diagnostic agent disclosed in Grenfell with about 0.0018 mg to about 0.45 mg of an alpha adrenergic receptor antagonist when Watt-Smith teaches away from the use of lower doses and concentrations.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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EXHIBIT A

Introducing dose-response curves

What is a dose-response curve?

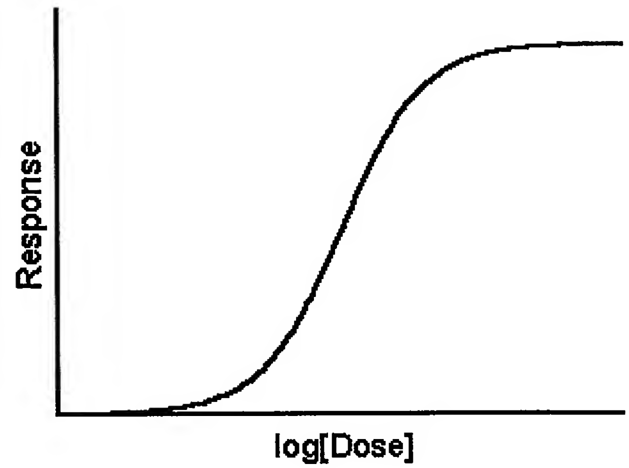
Dose-response curves can be used to plot the results of many kinds of experiments. The X-axis plots concentration of a drug or hormone. The Y-axis plots response, which could be almost anything. For example, the response might be enzyme activity, accumulation of an intracellular second messenger, membrane potential, secretion of a hormone, heart rate or contraction of a muscle.

The term "dose" is often used loosely. The term "dose" strictly only applies to experiments performed with animals or people, where you administer various doses of drug. You don't know the actual concentration of drug -- you know the dose you administered. However, the term "dose-response curve" is also used more loosely to describe *in vitro* experiments where you apply known concentrations of drugs. The term "concentration-response curve" is a more precise label for the results of these experiments. The term "dose-response curve" is occasionally used even more loosely to refer to experiments where you vary levels of some other variable, such as temperature or voltage.

An *agonist* is a drug that causes a response. If you administer various concentrations of an agonist, the dose-response curve will go uphill as you go from left (low concentration) to right (high concentration). A *full agonist* is a drug that appears able to produce the full tissue response. A *partial agonist* is a drug that provokes a response, but the maximum response is less than the maximum response to a full agonist. An *antagonist* is a drug that does not provoke a response itself, but blocks agonist-mediated responses. If you vary the concentration of antagonist (in the presence of a fixed concentration of agonist), the dose-response curve will run downhill.

The shape of dose-response curves

Many steps can occur between the binding of the agonist to a receptor and the production of the response. So depending on which drug you use and which response you measure, dose-response curves can have almost any shape. However, in very many systems dose-response curves follow a standard shape,



shown below.

Dose-response experiments typically use 10-20 doses of agonist, approximately equally spaced on a logarithmic scale. For example doses might be 1, 3, 10, 30, 100, 300, 1000, 3000, and 10000 nM. When converted to logarithms, these values are equally spaced: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0.

Note: The logarithm of 3 is actually 0.4771, not 0.50. The antilog of 0.5 is 3.1623. So to make the doses truly equally spaced on a log scale, the concentrations ought to be 1.0, 3.1623, 10.0, 31.623 etc.

Since the linkage between agonist binding and response can be very complex, any shape is possible. It seems surprising, therefore, that so many dose-response curves have shapes identical to receptor binding curves. The simplest explanation is that the link between receptor binding and response is direct, so response is proportional to receptor binding. However, in most systems one or more second-messenger systems link receptor binding to response. For example, agonist binding activates adenylyl cyclase, which creates the second-messenger cAMP. The second messenger can then bind to an effector (such as a protein kinase) and initiate a response.

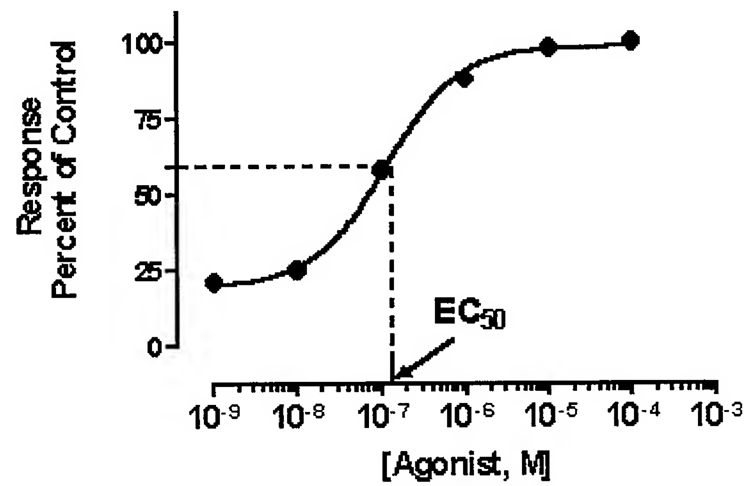
What do you expect a dose-response curve to look like if a second messenger mediates the response? If you assume that the production of second messenger is proportional to receptor occupancy, the graph of agonist concentration vs. second messenger concentration will have the same shape as receptor occupancy (a hyperbola if plotted on a linear scale, a sigmoid curve with a slope factor of 1.0 if plotted as a semilog graph). If the second messenger works by binding to an effector, and that binding step follows the law of mass action, then the graph of second messenger concentration vs. response will also have that same standard shape. It isn't obvious, but Black and Leff (see The operational model of agonist action) have shown that the graph of agonist concentration vs. response will also have that standard shape (provided that both binding steps follow the law of mass action). In fact, it doesn't matter how many steps intervene between agonist binding and response. So long as each messenger binds to a single binding site according to the law of mass action, the dose-response curve will follow the same hyperbolic/sigmoid shape as a receptor binding curve.

The EC_{50}

A standard dose-response curve is defined by four parameters: the baseline response (Bottom), the maximum response (Top), the slope, and the drug concentration that provokes a response halfway between baseline and maximum (EC_{50}).

It is easy to misunderstand the definition of EC_{50}. It is defined quite simply as the concentration of agonist that provokes a response half way between the baseline (Bottom) and maximum response (Top). It is impossible to define the EC_{50} until you first define the baseline and maximum response.

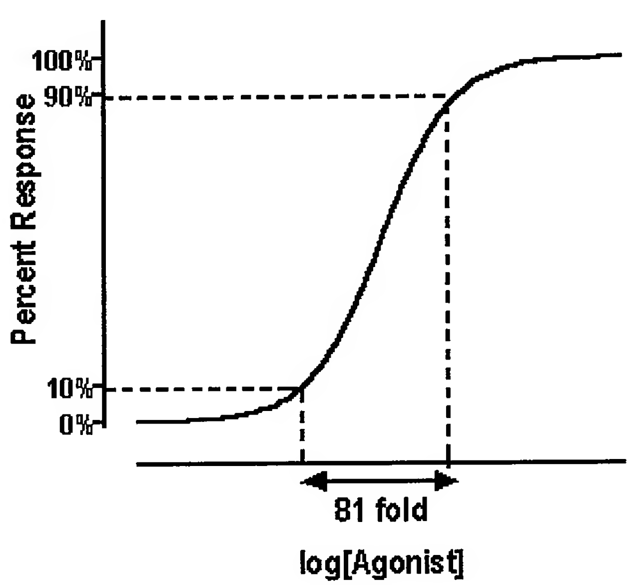
Depending on how you have normalized your data, this may not be the same as the concentration that provokes a response of Y=50. For example, in the example below, the data are normalized to percent of maximum response, without subtracting a baseline. The baseline is about 20%, and the maximum is 100%, so the EC_{50} is the concentration of agonist that evokes a response of about 60% (half way between 20% and 100%).



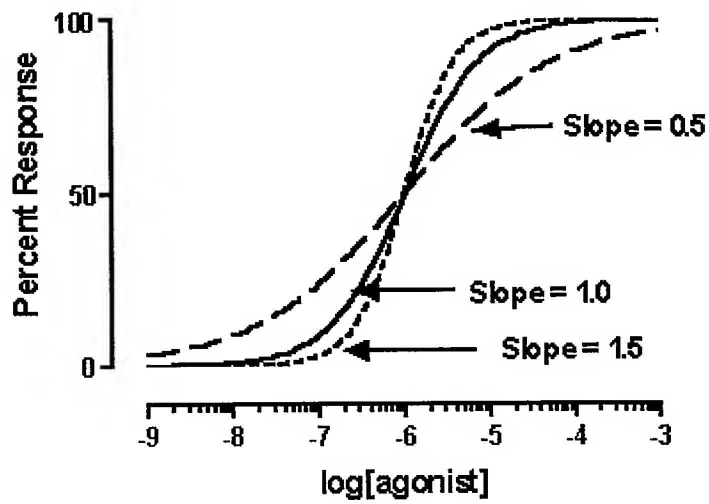
Don't over interpret the EC_{50}. It is simply the concentration of agonist required to provoke a response halfway between the baseline and maximum responses. It is usually not the same as the K_d for the binding of agonist to its receptor.

The steepness of a dose-response curve

Many dose-response curves follow exactly the shape of a receptor binding curve. As shown below, 81 times more agonist is needed to achieve 90% response than a 10% response.



Some dose-response curves however, are steeper or shallower than the standard curve. The steepness is quantified by the Hill slope, also called a slope factor. A dose-response curve with a standard slope has a Hill slope of 1.0. A steeper curve has a higher slope factor, and a shallower curve has a lower slope factor. If you use a single concentration of agonist and varying concentrations of antagonist, the curve goes downhill and the slope factor is



negative.

Fitting sigmoid dose-response curves with Prism